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California Morbidity

Department of Health Services
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CM is Back

If your last issue of **California Morbidity (CM)** was June 1997 (Prevention of Occupational Asthma in California: The SENSOR Project), you haven't missed any copies. For a variety of reasons we had to suspend publication of **CM**. But **we're back** again. **CM** will continue to be edited by the Division of Communicable Disease Control (DCDC) and continue to be a monthly publication. We want to feature the good work of local health departments and encourage submission of articles (see **Note to Authors** on back page).

Detection and Reporting of *Staphylococcus aureus* with Reduced Susceptibility to Vancomycin

Much has been written, including past **CM** notes (1-3), on vancomycin-resistant enterococci (VRE). Although VRE continues to represent an ongoing problem for hospitals and long-term care health facilities, the intrinsic low virulence of VRE makes these organisms a threat primarily to severely compromised patients. *Staphylococcus aureus* is a virulent organism capable of causing local, invasive, and systemic infections. While an important cause of nosocomial infections, particularly in its antibiotic-resistant forms, minor breaks in the skin can result in infections in any person. The development of resistance, first to penicillin, then to the methicillin-like drugs (methicillin-resistant *S. aureus* or MRSA), primarily in hospitalized patients but increasingly in community-acquired infections (4), has resulted in decreased efficacy and increased cost in treating these infections. For MRSA and multi-drug resistant *S. aureus* infections, vancomycin is often the only effective drug available. The development of vancomycin resistance in enterococci and the ability of the gene responsible for high-level resistance to be transferred in-vitro to *S. aureus*, and the emergence of vancomycin resistance in coagulase-negative staphylococci (CNS), have led to predictions of the eventual emergence of vancomycin-resistant *S. aureus* (VRSA). Laboratory studies previously demonstrated the ability of vancomycin to select for existing resistant subpopulations of both CNS and *S. aureus*. Interim guidelines for the control of staphylococcal infection associated with reduced susceptibility to vancomycin were published in advance of this occurrence in the United States (5) and are available on the Internet (www.cdc.gov/ncidod/hip/vanco/vanco.htm).

Occurrence of *S. aureus* with Reduced Susceptibility to Vancomycin

In May 1996, the first documented case of infection caused by *S. aureus* with reduced susceptibility to vancomycin was detected in a pediatric patient in Japan (6). After treatment of a surgical-site infection for several weeks with vancomycin and other antibiotics, an MRSA strain was isolated from the site that demonstrated a vancomycin minimum inhibitory concentration (MIC) of 8 µg/mL (National Committee for Clinical Laboratory Standards breakpoints: susceptible, ≤4 mg/mL; intermediate, 8–16 µg/mL; and resistant, ≥32 µg /mL) (7), so-called vancomycin-intermediate *S. aureus* or VISA. The organism was negative when tested by polymerase chain reaction for *vanA* and *vanB*, the principal genes responsible for vancomycin resistance in enterococci. It demonstrated homogeneous resistance (i.e., all members of the population exhibited resistance).

Subsequently, a strain of vancomycin-susceptible MRSA (MIC 3 µg/mL) was isolated from another patient in Japan with pneumonia after surgery who had failed vancomycin therapy (8). This strain had a pulsed-field gel electrophoresis banding pattern identical to that from the previous patient. However, it demonstrated heterogeneous resistance to vancomycin, producing subpopulations of cells with varying degrees of vancomycin resistance roughly proportional to the concentration of vancomycin present. When grown in media with 8 µg/mL or more of vancomycin, it gave rise to subclones of VISA (MIC 8µg/mL). Screening of additional MRSA isolates found that heterogeneously resistant VISA was found in hospitals throughout Japan, from 20% at the university

hospital where the original isolates were discovered, 9% at other university hospitals, to 1% in non-university hospitals or clinics. That MRSA infections in Japan frequently do not respond to vancomycin could be explained at least in part by this finding.

Two cases of infection with *S. aureus* intermediately resistant to vancomycin (VISA, MIC, 8 µg/mL) have been reported to date in the United States (9). #1: In July 1997, VISA-associated peritonitis was diagnosed in a Michigan resident who was being treated with long-term ambulatory peritoneal dialysis. During the previous six months the patient had been treated with multiple courses of both intraperitoneal and intravenous vancomycin for repeated episodes of vancomycin-susceptible, MRSA-associated peritonitis. The VISA isolate was, however, susceptible to chloramphenicol, rifampin, trimethoprim-sulfamethoxazole, and tetracycline. #2: In August 1997, a VISA-associated bloodstream infection was diagnosed in a New Jersey resident with long-term MRSA colonization and repeated MRSA infection with VRE colonization over the previous six months. The VISA isolate was, however, susceptible to gentamicin, trimethoprim-sulfamethoxazole, and tetracycline. Both patients continued to receive antimicrobial therapy at home. Whether VISA is already prevalent in the United States, as in Japan, has not yet been determined. VISA has not yet been reported in California, although VRE has become prevalent throughout the state over the past three years, and vancomycin-resistant CNS (*S. epidermidis*) has been detected, most recently in peritoneal fluid of a peritoneal dialysis patient receiving vancomycin for MRSA-associated peritonitis.

The impact of reduced vancomycin susceptibility on clinical outcome may be difficult to assess because serious infections caused by fully susceptible *S. aureus* often require treatment with a combination of aggressive surgical and antimicrobial therapy. It may be most evident in the treatment of infections at sites where achievable drug concentrations are lower than those commonly achieved in the bloodstream (e.g., closed space or central nervous system infections) or in treating infections in the presence of a foreign body. Patients with infections caused by *S. aureus* (i.e., MRSA) with reduced susceptibility to vancomycin and who unequivocally have not responded to appropriate therapy may be candidates for treatment with an investigational drug. CDC and the Food and Drug Administration are collaborating to make such agents available in the United States (see ref.5).

Surveillance for *S. aureus* with Reduced Susceptibility to Vancomycin

Surveillance is the single most important tool for identifying infectious diseases that are emerging and causing serious public health problems. Active surveillance is critical for the early detection and subsequent control of staphylococci with decreased susceptibility to vancomycin. The Division of Communicable Disease Control (DCDC) is working closely with local health departments, licensed health care facilities, and a variety of health care organizations, and the federal Centers for Disease Control and Prevention (CDC) Hospital Infections Program to ensure prompt identification and reporting of any isolations of this organism.

Personnel in hospitals should be particularly vigilant for the emergence of staphylococci with decreased susceptibility to vancomycin. Clinicians who believe they have identified patients infected with staphylococci with decreased susceptibility to vancomycin are asked to notify their local health departments and to ensure that the organism is retained in the laboratory for transfer to local health department, DHS, and CDC laboratories for confirmatory testing.

Detecting Staphylococci with Reduced Vancomycin Susceptibility

Use of recommended laboratory methods (including media and incubation methods, antimicrobial susceptibility testing methods, and susceptibility breakpoints) for identifying such strains is essential.

1. The most accurate antimicrobial susceptibility testing for staphylococci is a minimal inhibitory concentration method (broth dilution, agar dilution, or agar-gradient diffusion) using a full 24-hour incubation. Strains of staphylococci with a MIC=8 µg/mL (classified as intermediate using National Committee for Clinical Laboratory Standards breakpoints) were not detected by using the current disk diffusion procedure.

All strains with a MIC≥4 μg/mL should be considered candidate strains for reduced vancomycin susceptibility. Many *S. aureus* strains with putative reduced vancomycin susceptibility sent to CDC for confirmation have been misidentified or were not pure cultures. Therefore, the laboratory should ensure that the strain is not contaminated with other microorganisms and reconfirm the genus and species of the organism; then repeat the susceptibility test for vancomycin using a minimal inhibitory concentration method.

2. If, after repeat testing, species identification and vancomycin test results are consistent, immediately contact the local health department and DCDC (510/540-2566; nights and weekends 510/540-2308) to report presumptive identification of VISA. We will arrange for confirmatory testing.

Preventing the Spread of Staphylococci with Reduced Vancomycin Susceptibility

After repeat testing confirms the identification of staphylococci with reduced vancomycin susceptibility, the laboratory should immediately notify infection-control personnel, the clinical unit, and the attending physician. In turn, infection-control personnel should immediately notify the local health department, which will then notify DCDC (510/540-2566). An epidemiologic and laboratory investigation should be conducted by infection control personnel in consultation with local and state health departments, together with the institution of infection control measures as described in the CDC Interim Guidelines (5).

Preventing Further Spread of Resistance to Vancomycin (and other Antibiotics)

Following so quickly on the heels of the development of vancomycin resistance in enterococci, the emergence of VISA should serve as further warning for the need for antibiotic controls. Antimicrobial use is a major risk factor for the emergence of antimicrobial-resistant pathogens. Proper antimicrobial use will impede the spread of vancomycin resistance and decrease the risk of emergence of staphylococci with full resistance to vancomycin (i.e., MIC≥32 μg/mL). Medical and ancillary staff members who are responsible for pharmacy formulary decisions should review and restrict use of vancomycin (6) and ensure that use of other antimicrobials is appropriate as well. The time has come for everyone to work together to maintain our armamentarium of effective antimicrobial agents as long as we can.

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Note to Authors: Articles should be submitted to CM Editor, DCDC, CA Department of Health Services, 2151 Berkeley Way, Berkeley, CA 94704. Length should be approximately 1000 words or less. Tables, figures, and other materials can be included as supplements. Submit typed, double-spaced hard copy of text and tables along with electronic copies, preferably in Word or Wordperfect, Macintosh or Windows, on a floppy disk. Graphics may be in a graphic format. Acknowledgments as to source will be provided, and may be individuals and/or programs as suggested. Publication in *CM* should not preclude publication elsewhere.